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To:  
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RECEIVED  
- 4 SEP 2003  
BOULT WADE TENNANT

(PCT Article 17(3)(a) and Rule 40.1)

**AANGETEKEND/REGISTERED**

BOULT WADE TENNANT		Date of mailing (day/month/year)	02/09/2003
Applicant's or agent's file reference SCB/58858001		PAYMENT DUE	within 30 <del>months</del> days from the above date of mailing
International application No. PCT/GB 03/ 00034		International filing date (day/month/year)	07/01/2003
Applicant  NORCHIP A/S			

- (i) considers that there are 5 (number of) inventions claimed in the international application covered by the claims indicated ~~XXXX~~ on the extra sheet:

and it considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below/on the extra sheet:

- (ii) ☒ has carried out a partial international search (see Annex) ☐ will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:

1, 2, 11-16 (all partially)

- (iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid



2. The applicant is hereby **invited**, within the time limit indicated above, to pay the amount indicated below:

<u>EUR 945,00</u>	x	<u>4</u>	=	<u>EUR 3.780,00</u>
Fee per additional invention		number of additional inventions		total amount of additional fees

Or, \_\_\_\_\_ x \_\_\_\_\_ = \_\_\_\_\_

The applicant is informed that, according to Rule 40.2(c), **the payment of any additional fee may be made under protest, i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.**

3. ☐ Claim(s) Nos. \_\_\_\_\_ have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Gwenaëlle L. M. 
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This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1, 2, 11-16 (all partially)

Invention 1: Methods to assess the risk of developing cervical carcinoma based on the detection of E6 mRNA AND L1 mRNA. Kits to carry out said methods.

2. Claims: 3 (complete); 11-16 (all partially)

Invention 2: Methods to assess the risk of developing cervical carcinoma based on the detection of E6 mRNA AND p16-INK4a mRNA. Kits to carry out said methods.

3. Claims: 6-10, 12-16 (all partially)

Invention 3: Methods to assess the risk of developing cervical carcinoma based on the detection of E6 mRNA ALONE. Kits to carry out said methods.

4. Claims: 4, 10-16 (all partially)

Invention 4: Methods of screening for the presence of integrated HPV based on the detection of HPV E6 mRNA AND L1 mRNA. Kits to carry out said methods.

5. Claims: 5, 8-10, 12-16 (all partially)

Invention 5: Methods of screening for the presence of integrated HPV based on the detection of HPV E6 mRNA ALONE. Kits to carry out said methods.

The common concept disclosed in the application can be considered as screening methods based on the detection of E6 mRNA.

However, this concept is not new in view of EP0373352 (BEHRINGWERKE AG; 20.06.1990), which discloses a method of detection of HPV E6 mRNA by RT-PCR (see Abstract and pages 2-5).

In view of this prior art, the problem to be solved by the present invention can be considered as providing further uses to the detection of HPV E6 mRNA. The solutions given by the present application are: (a) methods to assess and categorize the risk of developing cervical carcinoma; and (b) methods to screen for the presence of an integrated HPV or a modified episomal HPV genome.

Because no other technical features can be distinguished which, in view of the prior art could be regarded as special technical features in the sense of Rule 13.2 PCT, the ISA is of the opinion that there is no single inventive concept underlying the plurality of claimed inventions of the present application in the sense of rule 13.1 PCT. Consequently, there is a lack of unity, and the methods (a) and (b) are different groups of inventions not belonging to a common inventive

concept.

Considering now the first group of inventions (a), the common concept can be considered as methods to assess the risk of developing cervical carcinoma based on the detection of HPV E6 mRNA.

However, this concept is not new in view of EP0373352 (see above), which also discloses the assessment of said risk by detecting the HPV E6 mRNA (see Abstract and page 2, lines 1-35).

In view of this prior art, the problem to be solved by the present invention can be considered as providing further methods to assess the risk of developing cervical carcinoma based on the detection of HPV E6 mRNA. The solutions given by the present application are the different combinations of marker mRNAs to be detected: HPV E6 and HPV L1 mRNAs; HPV E6 and p16-INK4a mRNAs; or HPV E6 mRNA alone, excluding the detection of any other marker.

Because no other technical features can be distinguished which, in view of the prior art could be regarded as special technical features in the sense of Rule 13.2 PCT, the ISA is of the opinion that there is no single inventive concept underlying the plurality of claimed inventions of the present application in the sense of rule 13.1 PCT.

Consequently, there is a lack of unity, and the methods and products claimed comprise different groups of inventions not belonging to a common inventive concept.

Considering now the second group of inventions above (b), the common concept can be considered as methods to screen for the presence of an integrated HPV or a modified episomal HPV genome by detecting HPV E6 mRNA.

However, this concept is not new in view of EP0373352 (see above), which also discloses that the detection of increased levels of HPV E6 mRNA performed by the method correlates with the integration event of HPV into the host cell genome (see page 2, lines 13-27. In general, the fact that E6 expression is up-regulated upon integration of HPV is well known since many years (see for example Durst et al., 1985; or Pater and Pater, 1985; both cited in page 16 of the description), and it cannot be considered to provide novel and inventive common concept for said methods.

In view of this prior art, the problem to be solved by the present invention can be considered as providing further methods to screen for the presence of an integrated HPV or a modified episomal HPV genome. The solutions given by the present application are the different combinations of marker mRNAs to be detected: HPV E6 and HPV L1 mRNAs; or HPV E6 mRNA alone, excluding the detection of any other marker.

The ISA has searched the first invention listed above 1, 2, 11-16 (all partially).

**Annex to Form PCT/ISA/206  
COMMUNICATION RELATING TO THE RESULTS  
OF THE PARTIAL INTERNATIONAL SEARCH**

International Application No

PCT/03/00034

1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:  
see 'Invitation to pay additional fees'
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.
3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.
4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 73135 A (MOLODYSKY EUGEN ; BIOSEARCH INTERNAT PTY LTD (AU); CORD JANET I (US) 4 October 2001 (2001-10-04) the whole document ----	1,2, 11-16
X	WO 99 29890 A (DIGENE CORP ; LORINCZ ATTILA T (US)) 17 June 1999 (1999-06-17) page 1 -page 15 ----	1,2, 11-16
X	LANHAM S ET AL: "HPV detection and measurement of HPV 6, telomerase and survivin transcripts in colposcopy clinic patients" JOURNAL OF CLINICAL PATHOLOGY, LONDON, GB, vol. 54, no. 4, April 2001 (2001-04), pages 304-308, XP002961294 ISSN: 0021-9746 the whole document ----	1,2, 11-16
Y	IWASAWA A ET AL: "HUMAN PAPILLOMAVIRUS DNA IN UTERINE CERVIX SQUAMOUS CELL CARCINOMA AND ADENOCARCINOMA DETECTED BY POLYMERASE CHAIN REACTION" CANCER, AMERICAN CANCER SOCIETY, PHILADELPHIA, PA, US, vol. 77, no. 11, 1 June 1996 (1996-06-01), pages 2275-2279, XP001053522 ISSN: 0008-543X the whole document ----- -/--	1,2, 11-16



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

**Annex to Form PCT/ISA/206  
COMMUNICATION RELATING TO THE RESULTS  
OF THE PARTIAL INTERNATIONAL SEARCH**

International Application No  
PC 03/00034

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KADO SATOSHI ET AL: "Detection of human papillomaviruses in cervical neoplasias using multiple sets of genetic polymerase chain reaction primers." GYNECOLOGIC ONCOLOGY, vol. 81, no. 1, April 2001 (2001-04), pages 47-52, XP002251986 ISSN: 0090-8258 the whole document	1,2, 11-16
Y	US 5 639 871 A (BAUER HEIDI M ET AL) 17 June 1997 (1997-06-17) page 6, line 41 -page 58, line 50	1,2, 11-16
A	EP 0 373 352 A (BEHRINGWERKE AG) 20 June 1990 (1990-06-20) page 1 -page 4	

# Patent Family Annex

Information on patent family members

International Application No

PCT/83 03/00034

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0173135	A	04-10-2001	AU 4952601 A WO 0173135 A2 US 2002132227 A1	08-10-2001 04-10-2001 19-09-2002
WO 9929890	A	17-06-1999	AU 748022 B2 AU 1723299 A AU 746061 B2 AU 1911799 A BR 9814271 A BR 9814272 A CA 2313483 A1 CA 2313641 A1 EP 1038029 A2 EP 1038022 A2 JP 2001526045 T JP 2002508190 T NO 20002979 A NO 20002980 A WO 9931273 A2 WO 9929890 A2 US 2003091992 A1 US 2001051364 A1 US 2002127545 A1 US 6355424 B1	30-05-2002 05-07-1999 11-04-2002 28-06-1999 20-03-2001 03-10-2000 17-06-1999 24-06-1999 27-09-2000 27-09-2000 18-12-2001 19-03-2002 09-08-2000 08-08-2000 24-06-1999 17-06-1999 15-05-2003 13-12-2001 12-09-2002 12-03-2002
US 5639871	A	17-06-1997	US 5447839 A US 5182377 A US 5527898 A US 5705627 A AT 138108 T AU 645483 B2 AU 4401189 A CA 1339262 C DE 68926507 D1 DE 68926507 T2 EP 0433396 A1 JP 2651483 B2 JP 4500910 T WO 9002821 A1 US 5283171 A	05-09-1995 26-01-1993 18-06-1996 06-01-1998 15-06-1996 20-01-1994 02-04-1990 12-08-1997 20-06-1996 16-01-1997 26-06-1991 10-09-1997 20-02-1992 22-03-1990 01-02-1994
EP 0373352	A	20-06-1990	DE 3838269 A1 AT 133715 T AU 627517 B2 AU 4460489 A CA 2002776 A1 DE 58909587 D1 DK 564089 A EP 0373352 A2 ES 2083371 T3 FI 100474 B1 JP 2187000 A JP 3375623 B2 US 5750334 A	17-05-1990 15-02-1996 27-08-1992 17-05-1990 11-05-1990 14-03-1996 12-05-1990 20-06-1990 16-04-1996 15-12-1997 23-07-1990 10-02-2003 12-05-1998